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(21) International Application Number: PCT/US97/18508 (22) International Filing Date: 14 October 1997 (14.10.97) (30) Priority Data: 08/735,290 22 October 1996 (22.10.96) US (71) Applicant: THE PROCTER & GAMBLE COMPANY [US/US]; One Procter & Gamble Plaza, Cincinnati, OH 45202 (US). (72) Inventor: SINGER, Robert, Ernest, Jr.; 8700 Ma- son-Montgomery Road, Mason, OH 45040 (US). (74) Agents: REED, T., David et al.; The Procter & Gamble Company, 5299 Spring Grove Avenue, Cincinnati, OH 45217 (US).		(81) Designated States: AU, BR, CA, CN, KR, MX, SG, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: ORAL COMPOSITIONS CONTAINING STANNOUS GLUCONATE (57) Abstract Oral compositions containing stannous gluconate to provide protection against colds and flu.		

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ORAL COMPOSITIONS CONTAINING STANNOUS GLUCONATE

TECHNICAL FIELD

The present invention relates to a method of preventing or controlling colds and similar maladies, such as flu, through the use of an oral composition containing stannous gluconate applied to the gingival or oral mucosal tissue of the subject susceptible to colds.

BACKGROUND OF THE INVENTION

The common cold, although not usually a serious illness, is a highly prevalent, discomforting and annoying infliction. The term "common cold" is applied to minor respiratory illnesses caused by a variety of different respiratory viruses. While rhinoviruses are the major known cause of common colds, accounting for approximately 30 percent of colds in adults, viruses in several other groups are also important. While immune responses occur, and infection with some respiratory tract viruses therefore could be prevented by a vaccine, development of a polytypic vaccine to cover all possible agents is impractical. Thus, the problem of controlling acute upper respiratory disease presents complex challenges, and the long-desired discovery of a single cure for the common cold is an unrealistic expectation.

With rhinovirus infection, symptoms of nasal discharge, nasal congestion, and sneezing usually commence on the first day of illness and progress to maximum severity by the second or third day. The costs of treating colds with over-the-counter medications in the United States is estimated at an annual cost of over 1.5 billion dollars. The direct costs of treatment in outpatient clinics is estimated at almost four billion dollars. Indirect costs, based on the amount of loss in wages because of restricted activity are substantially higher.

At present, only symptomatic treatment is available for the common cold; the majority of these drugs are taken orally. Exemplary prior art oral compositions for treatment of nasal and other cold, flu, allergy and sinus symptoms and the discomfort, pain, fever and general malaise associated therewith generally contain an analgesic (aspirin or acetaminophen) and one or more antihistamines, decongestants, cough suppressants, antitussives and expectorants. Other specific pharmaceutical actives for nasal symptoms (e.g., congestion) generally contain either oxymetazoline or phenylephrine. These actives are generally delivered topically to the nasal mucosa via a nasal spray. For individuals with certain medical conditions such as heart disease, hypertension, diabetes or thyroid disorders, oral drugs such as decongestants could pose a risk of unfavorable drug interactions and may cause an adverse reaction.

It would, therefore, be highly desirable to deliver relief from specific nasal symptoms via compositions without the need for such pharmaceutical actives.

It has been discovered that topical application of stannous gluconate to the gingival or oral mucosal tissues of a subject susceptible to colds and/or flu helps to reduce the incidence of such maladies.

It is therefore an object of the present invention to provide topical oral compositions which provide treatment to prevent colds and flu.

SUMMARY OF THE INVENTION

The present invention relates to a method of reducing colds and cold-like symptoms, such as flu, in subjects susceptible to such maladies by applying a composition containing an effective amount of stannous gluconate to the gingival or oral mucosal tissues.

DETAILED DESCRIPTION OF INVENTION

The compositions of the present invention contain certain essential components as well as non-essential components.

Stannous Gluconate

Stannous gluconate is an essential component of the present compositions. This material is a known stannous chelate and may be provided to the present compositions as the chelate or as separate soluble stannous and gluconate salts and the chelate formed in-situ. Such salts include stannous chloride and sodium gluconate. Stannous gluconate is present in the present compositions at a level of from about 0.1% to about 11%, preferably from about 0.2% to about 4%.

Acceptable Carrier

The carrier for the active component(s) can be any vehicle suitable for use in the oral cavity. Such carriers include the usual components of mouthwashes, gargles, toothpastes, tooth powders, prophylaxis pastes, lozenges, gums and the like and are more fully described hereinafter. Dentifrices and mouthwashes are the preferred systems.

In addition to the active agent(s), the present compositions may contain antiplaque/gingivitis agents such as quaternary ammonium compounds, water insoluble agents such as triclosan, teas, as defined herein later, stannous salts and zinc salts. These types of agents are described in U.S. patent 4,894,220; January 16, 1990 to Nabi et al, U.S. Patent 4,656,031, April 7, 1987 to Lane et al; and U.S. Patent 5,004,597, April 2, 1991 to Majeti et al. All incorporated herein by reference in their entirety.

The abrasive polishing material contemplated for use in the present invention can be any material which does not excessively abrade dentin. These include, for

example, silicas including gels and precipitates, calcium carbonate, dicalcium orthophosphate dihydrate, calcium pyrophosphate, tricalcium phosphate, calcium polymetaphosphate, insoluble sodium polymetaphosphate, hydrated alumina, and resinous abrasive materials such as particulate condensation products of urea and formaldehyde, and other such as disclosed by Cooley et al. in U.S. Patent 3,070,510, December 25, 1962, incorporated herein by reference. Mixtures of abrasives may also be used.

Silica dental abrasives, of various types, can provide the unique benefits of exceptional dental cleaning and polishing performance without unduly abrading tooth enamel or dentin. Silica abrasive materials are also exceptionally compatible with sources of soluble fluoride and polyphosphonates. For these reasons they are preferred for use herein.

The silica abrasive polishing materials useful herein, as well as the other abrasives, generally have an average particle size ranging between about 0.1 to 30 microns, preferably 5 and 15 microns. The silica abrasive can be precipitated silica or silica gels such as the silica xerogels described in Pader et al., U.S. Patent No. 3,538,230, issued March 2, 1970 and DiGiulio, U.S. Patent No. 3,862,307, June 21, 1975, both incorporated herein by reference. Preferred are the silica xerogels marketed under the tradename "Syloid" by the W. R. Grace & Company, Davison Chemical Division. Preferred precipitated silica materials include those marketed by the J. M. Huber Corporation under the tradename, "Zeodent", particularly the silica carrying the designation "Zeodent 119". These silica abrasives are described in U.S. Patent No. 4,340,583, July 29, 1982, incorporated herein by reference.

The abrasive in the compositions described herein is present at a level of from about 6% to about 70%, preferably from about 15% to about 25% when the dentifrice is a toothpaste. Higher levels, as high as 90%, may be used if the composition is a toothpowder.

The compositions of the present invention may also contain a soluble fluoride ion source such as sodium, potassium, lithium fluorides, stannous fluoride, and sodium monofluorophosphate among many others. The fluoride source should be sufficient to provide from about 50 to about 3500 ppm fluoride in a toothpaste or mouthrinse.

Flavoring agents can also be added to dentifrice compositions. Suitable flavoring agents include, among many others, oil of wintergreen, oil of peppermint, oil of spearmint, and oil of clove. Sweetening agents which can be used include aspartame, acesulfame, saccharin, dextrose, levulose and sodium cyclamate. Flavoring and sweetening agents are generally used in dentifrices at levels of from

about 0.005% to about 2% by weight.

Dentifrice compositions can also contain emulsifying agents. Suitable emulsifying agents are those which are reasonably stable and foam throughout a wide pH range, including nonsoap anionic, nonionic, cationic, zwitterionic and amphoteric organic synthetic detergents. Many of these suitable surfactants are disclosed by Gieske et al. in U.S. Patent No. 4,051,234, September 27, 1977, incorporated herein in its entirety by reference.

Water is also present in the toothpastes of this invention. Water employed in the preparation of commercially suitable toothpastes should preferably be deionized and free of organic impurities. Water generally comprises from about 10% to 50%, preferably from about 20% to 40%, by weight of the toothpaste compositions herein. These amounts of water include the free water which is added plus that which is introduced with other materials such as with sorbitol.

In preparing toothpastes, it is necessary to add some thickening material to provide a desirable consistency. Preferred thickening agents are carboxyvinyl polymers of the type mentioned previously herein, xanthan gum, carrageenan, hydroxyethyl cellulose and water soluble salts of cellulose ethers such as sodium carboxymethyl cellulose and sodium carboxymethyl hydroxyethyl cellulose. Natural gums such as gum karaya, gum arabic, and gum tragacanth can also be used. Colloidal magnesium aluminum silicate or finely divided silica can be used as part of the thickening agent to further improve texture. Thickening agents in an amount from 0.5% to 5.0% by weight of the total composition can be used.

It is also desirable to include some humectant material in a toothpaste to keep it from hardening. Suitable humectants include glycerin, sorbitol, xylitol, and other edible polyhydric alcohols at a level of from about 5% to about 70%.

Another preferred embodiment of the present invention is a mouthwash composition. Conventional mouthwash composition components can comprise the carrier for the active agents of the present invention. Mouthwashes generally comprise from about 20:1 to about 2:1 of a water/ethyl alcohol solution and preferably other ingredients such as flavor, sweeteners, humectants and sudsing agents such as those mentioned above for dentifrices. The humectants, such as glycerin and sorbitol give a moist feel to the mouth. Generally, on a weight basis the mouthwashes of the invention comprise 0% to 60% (preferably 10% to 25%) ethyl alcohol, 0% to 20% (preferably 5% to 20%) of a humectant, 0% to 2% (preferably 0.01% to 0.15%) emulsifying agent, 0% to 0.5% (preferably 0.005% to 0.06%) sweetening agent such as saccharin, 0% to 0.3% (preferably 0.03% to 0.3%) flavoring agent, and the balance water.

Suitable lozenge and chewing gum components are disclosed in U.S. Patent No. 4,083,955, April 11, 1978 to Grabenstetter et al., incorporated herein by reference.

Other optional components useful in the present invention are pyrophosphate salts such as those described in U.S. 4,515,772, May 7, 1985 to Parran et al. incorporated herein by reference. Also useful are nonionic antimicrobials such as triclosan described in U.S. 4,894,220, January 16, 1990 to Nabi et al. Both patents are incorporated herein by reference.

Another agent which can be used in the present compositions is an alkali metal bicarbonate, such as sodium bicarbonate. These are stable items of commerce and can be used together with a peroxide compound in separate compartments such as disclosed in U.S. 4,849,213 and U.S. 4,528,180, both to Schaeffer, incorporated herein by reference in its entirety.

Other preferred compositions of the subject invention are controlled-release drug delivery systems for placement in the periodontal pocket. Such systems include, but are not limited to, the cellulose hollow fibers disclosed in U.S. Pat. No. 4,175,326, issued to Goodson on Nov. 27, 1979; the ethylcellulose films disclosed in U.S. Pat. No. 4,568,535 issued to Loesche on Feb. 4, 1986; the absorbable putty-like material disclosed in U.S. Pat. No. 4,568,536 issued to Kronenthal, Maftai and Levy on Feb. 4, 1986; the biodegradable microspheres and matrix disclosed in U.S. Pat. No. 4,685,883 issued to Jernberg on Aug. 11, 1987; the microparticle or microcapsule suspensions disclosed in U.S. Pat. No. 4,780,320 issued to Baker on Oct. 25, 1988; the polymeric devices disclosed in European Patent Application No. 0,140,766 of Goodson, published May 8, 1985; and the lactide/glycolide executions described in U.S. Patent No. 5,198,220, March 30, 1993 to Damani; these patents are incorporated herein by reference. Such controlled-release delivery systems generally include a solid matrix, usually of polymeric material, loaded with one or more active agents, the matrix entrapping stannous gluconate. Typically, the active agents diffuse from the solid material into the periodontal pocket over time.

Preferred controlled-release drug delivery systems comprise from about 0.001% to about 50%, more preferably from about 0.01% to about 25%, more preferably still from about 0.1% to about 15%, still more preferably from about 1% to about 10%, of stannous gluconate and a controlled-release carrier.

The pH of the present compositions and/or its pH in the mouth can be any pH which is safe for the mouth's hard and soft tissues. Such pH's are generally from about 3 to about 10, preferably from about 5 to about 9.

METHOD OF MANUFACTURE

The carrier compositions of the present invention can be made using methods which are common in the oral products area.

For example, toothpaste compositions may be prepared by mixing part of the humectant and water together and heating to 66°-71°C. The fluoride source, if present, is then added along with the sweetener, the opacifier and the flavor.

COMPOSITIONS OF USE

The present invention in its method aspect involves applying to the gingival and/or oral mucosal tissue safe and effective amounts of the compositions. Generally an amount of at least about 5 grams of a mouthwash and at least about 0.5 of a toothpaste or liquid dentifrice.

A preferred method of the subject invention involves the contact of a composition of the subject invention with oral cavity soft tissue for at least about 15 seconds, preferably from about 20 seconds to about 10 minutes, more preferably from about 30 seconds to about 60 seconds. The method often involves expectoration of most of the composition following such contact, preferably followed by rinsing, e.g., with water. The frequency of such contact is preferably from about once per week to about five times per day, more preferably from about thrice per week to about four times per day, more preferably still from about once per day to about thrice per day. The period of such treatment typically ranges from about one day to a lifetime. Generally, people may recognize that they will be exposed to a cold's virus and they then can use the products described herein either prior to the exposure, following exposure, or at the first signs of a cold.

The compositions used in the present method may also be used by the subject as a gargle. Additionally, subjects taking significant doses of Vitamin C may achieve an enhanced colds benefit through the use of the compositions described herein.

The following examples further describe and demonstrate preferred embodiments within the scope of the present invention. The examples are given solely for illustration and are not to be construed as limitations of this invention as many variations thereof are possible without departing from the spirit and scope thereof.

EXAMPLE I**Toothpastes**

	<u>Weight %</u>	<u>Weight %</u>
Water	13.017	12.500
Sorbitol	45.425	44.552
Glycerin	10.198	10.198
Titanium Dioxide	0.525	0.525
Silica	20.000	20.000
Na Carboxymethyl Cellulose	1.050	1.050
Magnesium Aluminum Silicate	0.408	0.408
Na Alkyl Sulfate (27.9% Solution)	4.000	4.000
Na Gluconate	1.738	3.476
Stannous Chloride Dihydrate	1.794	1.794
Na Saccharin	0.200	0.200
Flavor	0.851	0.851
FD&C Blue #1 (1% Solution)	0.051	0.051
Sodium Fluoride	0.243	-
Na Hydroxide (50% Solution)	0.500	0.395
pH	4.5	4.5

EXAMPLE II**Mouthrinses**

	<u>Weight %</u>	<u>Weight %</u>
Stannous Chloride Dihydrate	0.519	0.519
Sodium Gluconate	0.521	1.041
Glycerin	8.000	12.000
Sorbitol (70% Aqueous Solution)	-	-
Ethanol	10.000	10.000
Polysorbate 80	0.300	0.300
Sodium Saccharin	0.050	0.050
Flavor	0.150	0.150
Sodium Hydroxide	0.020	0.020
Benzoic Acid	0.050	0.050
FD&C Blue #1 (1% Solution)	0.020	0.020
Sodium Monofluoro Phosphate	0.183	-
Water	80.187	77.850

EXAMPLE III**Topical Gels**

	<u>Weight %</u>	<u>Weight %</u>
Stannous Chloride Dihydrate	1.794	2.153
Sodium Gluconate	1.750	2.082
Glycerin	91.896	70.000
Sorbitol (70% Solution)	-	21.765
Sodium Carboxymethyl Cellulose	0.600	0.800
Hydroxyethyl Cellulose	-	-
Flavor	1.000	1.000
Sodium Saccharin	0.200	0.200
Sodium Alkyl Sulfate (27.9%)	2.000	2.000
Sodium Monofluoro Phosphate	0.760	-

EXAMPLE IV**Mouthrinse Tablets**

Stannous Chloride Dihydrate	0.519g	0.519g
Sodium Gluconate	0.500g	0.700g
Flavor	0.150g	0.150g
Sodium Saccharin	0.050g	0.200g
Mannitol	0.773g	-
Sodium Carboxymethyl Cellulose	0.050g	-
Sodium Benzoate	0.030g	0.025g
Citric Acid	-	0.200g
Sodium Carbonate	-	0.100g
Sodium Bicarbonate	-	0.200g
Glycine	-	0.050g
Sodium Monofluoro Phosphate	<u>0.183g</u>	<u>-</u>
	2.255g	2.144g
	Dissolve	Dissolve
	in 97.745g	in 97.856g
	water	water

What is claimed is:

1. A method of reducing the incidence of colds and similar maladies, such as flu, in animals susceptible to colds comprising applying to the gingival and/or oral mucosal tissue of said animal an effective amount of a composition containing an effective amount of stannous gluconate.
2. A method according to Claim 1 wherein said composition is in the form of a toothpaste.
3. A method according to Claim 1 wherein said composition is in the form of a mouthrinse.
4. A method according to Claim 1 wherein said composition is in the form of a site specific delivery system.
5. A method according to Claim 1 wherein the concentration of stannous gluconate is from about 0.1% to about 11%.
6. A method according to Claim 2 wherein said toothpaste contains a silica abrasive.
7. A method according to Claim 6 which in addition contains another stannous salt.
8. A method according to either of Claims 6 or 7 which in addition contains a fluoride ion source.
9. A method according to any of Claims 6-8 which in addition contains an agent selected from the group consisting of surfactants, humectants, sweetening agents and mixtures thereof.
10. A method according to any of Claims 6-9 wherein the humectant is selected from the group consisting of sorbitol, glycerin, xylitol and mixtures thereof.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/18508

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K7/16

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 281 411 A (S.MAJETI,C.B.GUAY,M.CRISANTI) 25 January 1994 see claims 1-6 see column 3, line 40-47 see column 4, line 31-52 ---	1-10
X	WO 93 07852 A (PROCTER & GAMBLE) 29 April 1993 see claims 1-8 see page 5, line 20-31 see page 6, line 29-32 see page 7, line 8-22 ---	1-10
X	WO 93 07850 A (PROCTER & GAMBLE) 29 April 1993 see claims 1-8 see page 7, line 5-15 ---	1-10

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Peeters, J

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/18508

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 338 537 A (D.J.WHITE,E.R.COX,R.CASTURI) 16 August 1994 see claims 1,4 see column 5, line 36 - column 6, line 58 see column 7, line 3-7 see column 7, line 22-40 ----	1-10
X	EP 0 311 260 A (PROCTER & GAMBLE) 12 April 1989 see claims 1-8,11 see page 4, line 37-54 X & US 5 004 597 A cited in the application ----	1-10
X	EP 0 311 259 A (PROCTER & GAMBLE) 12 April 1989 see claims 1-9,12 see page 4, line 24-58 see page 5, line 1-10 ----	1-10
X	GB 779 504 A (AMERICAN CYANAMID) 24 July 1957 see claims 1-4 see page 2, line 57-74 see example 35 -----	1-4